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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,365	03/06/2002	Eiji Ozaki	P 290686	3065

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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER
REYES, HECTOR M

ART UNIT	PAPER NUMBER
1625	7

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,365	Applicant(s) OZAKI ET AL.	
	Examin r Hector M Reyes	Art Unit 1625	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 to 4 and 44 to 82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 to 4 and 44 to 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 and 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Paper Entry

Examiner acknowledges the following Papers:

- Information Disclosure Statement, filed on March 6, 2002 as paper no. 2
- PCT/DE/EO/903 form, filed on May 8, 2002 as paper no. 3
- Preliminary Amendment, filed March 6, 2002 as Paper no. 4
- Preliminary Amendment filed on May 24, 2002 as Paper no. 5
- Information Disclosure Statement, filed on July 17, 2002 as Paper no. 6.

Status of The Claims

Claims 5 through 43 had been canceled. New claims 44 through 82 had been added. Currently, claims 1 to 4 and 44 to 82 are under Examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 44-51, 53-55; 57-70, 72-78 80-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, ***while being enabling for a optical resolution of 4-amino-2-methylbutane-1-ol with the following optically active compounds or the corresponding diastereomeric salt from the said amino alcohol:***

- (R)-2-choromandelic acid
- (R) –4-chloromandelic acid

- (R)-4-nitromandelic acid
- (S)-2-chloromandelic acid
- (+) –10-camphorsulfonic acid
- (S) –(-)-3-phenylllacetic acid N-acetyl-D-valine

Does not reasonably provide enablement for the

I. The use of any other:

- Optically active carboxylic acid,
- Optically active sulfonic acid or
- Optically active phosphonic acids

II. The preparation of any other diastereomeric salts

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. See MPEP 2164.01

Some of the factors considered ion the present rejection are:

The Nature of the Invention

The broadest interpretation of the instant invention is drawn to:

- Optical resolution of 4-amino-2-methylbutane-1-ol, via the formation of a diastereoisomers of the said amino alcohol with any optically active acid, including non carboxylic acid substance,
- Acid base treatment of the diastereoisomeric salt in order to recover the desired optically active amino alcohol and the resolving agent
- Process of using the optically active amino alcohol in synthetic procedures

The broader interpretation of the said process included no limitations in essential parameters or limitations such as:

- Type of solvent or combination of solvents required in crystallization or re-crystallization
- Reaction conditions such as crystallization temperature and time
- Specific optically active acid needed in order to form the required diastereoisomeric salts.

The State of the Prior Art

To those skilled in the art, the optical resolution of a given substance containing an amino group can be, in theory, carry out by means of an optically active acid via a general and conventional process that would requires:

- A pure optically acid
- A selection of a convenient solvent or solvent combination
- Enantiomeric-salt formation and separation, usually via crystallization
- Recovery of optically active substances that compose each particular enantiomer via acid-base process.

Nonetheless, not within the domain of those skilled in the art are the specific reactants, reactions conditions and solvent or solvent combinations that would successfully works in a resolution of a specific chiral amine.

The said process is one wherein the physical characteristic of the said enantiomers and the solubility of the said are essential in the said process.

The closer prior art found teaches that (-)-2-amino–1-butanol is a resolving agent for the optical separation of racemic mandelic acid in water or lower alcohol or mixture thereof, therefore suggesting that enantiomeric salts of mandelic acid and the amino alcohols have physical characteristics which facilitates the enantiomers resolution via the separation of the corresponding diastereoisomers. (See US patent 4259521) The prior art does not disclose or suggest the use of other diastereoisomeric salts having other acid as counter anion.

A patent granting such a general optical resolution process would obscure a research area, without any benefit to the public.

The level of Predictability in the Art

There is no predictability that any possible optically acid would indeed form a convenient pair of enantiomers that are separated by any method of separation in any solvent or solvent combination. Resolution parameters are indeed quite specific and very unlikely to be predictable base upon general knowledge of similar optically active acids, even more if the claimed acids are not even similar to those disclosed in the working examples. Predictability would demand similar chemical structure in:

- The resolving agent and the racemic mixture to be resolve,
- The diastereoisomeric salts subjected to separation and
- The solvent(s) use in the resolution process.

The existence of working examples

The working examples only enable for the use of the following optically active acids:

- (R)-2-choromandelic acid

- (R) –4-chloromandelic acid
- (R)-4-nitromandelic acid
- (S)-2-chloromandelic acid
- (+) –10-camphorsulfonic acid
- (S) –(-)-3-phenylllacetic acid N-acetyl-D-valine

Using the following organic solvents:

methanol, isopropanol, n-propanol, ethanol, acetone, acetonitrile.

Experimentation required to make the invention

In order to carry out the instant invention as being claimed, it would be necessary to prepared

- An extensive number of optically active acid-including carboxylic acids, sulfonic acids and phosphonic acids having a highly purity
- Prepared the corresponding diastereoisomers in extensive solvents and combination of solvents in different proportions
- Evaluate different separation techniques in order to pursue the successfully separation of the formed diastereoisomers. Determination of reaction parameters and evaluation of physical characteristics would be needed
- Use the said diastereoisomeric salts as optically active reagents
- Liberation of optically active materials once the diastereoisomers are separated.

Clearly, undue experimentation would be required in order to make and used the invention the invention commensurate in scope with these claims. See MPEP 2164.01 See In re Wands, 8 USPQ 2d 1400 and In re.Wright 27 USPQ 2d 1510.

Claim R j ctions - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 44, 49, 53, 57, 68 and 76, the phrase ***optically active organic acid*** is indefinite because the said acid is essential to the process and it is no properly characterized.

In claims 1 to 4 are indefinite because the required solvent or combination of solvents, as well as the separation technique required to separate the diastereoisomers are not described.

In claims 44 and 57 the phrase "by use of a solvent" is indefinite because the said solvent is essential to the process, and it is not identify.

In claims 46 and 59 the phrase "by using a solvent to obtain a diastereomeric salt" is indefinite because the essential solvent required is not identified.

In claim 48, the phrase "ion exchange resin" is indefinite because the composition of the said required ion exchange resin is not identified.

In claim 49 is indefinite because it is unclear what is the salt being claimed due to the fact that the organic acid part of the salt is not identify.

In claim 63 the phrase "optically active reagent for optically resolution" is indefinite because there is not identification of the said reagent. Moreover, optically active reagent may not be exclusively used in optical resolution processes.

In claims 64 and 65 the phrases

- " alkali salt of optically active reagent for optical resolution"
- "contact with a solvent"
- "optically active reagent for optical resolution"

are indefinite because it is unknown which are the specific limitations regarding the said alkali salt, solvent or optically active reagent.

In claim 66 the phrases

- "optically active reagent for optical resolution"
- "contact with an alcohol"
- "alkali metal alcoholate optically active reagent for optical resolution"

are indefinite because it is unknown which are the specific limitations regarding the said lakali salt, solvent or optically active reagent.

In claim 67 the phrases

- "optically active reagent for optical resolution"
- "contact with an alcohol"
- "alkali metal salt of the optically active reagent for optical resolution"

are indefinite because it is unknown which are the specific limitations regarding the said alkali salt, alcohol or optically active reagent. The use of the phrase and/or is also indefinite because the simultaneous use of inclusive and exclusive language.

In claims 72 and 73 the phrases

- "optically active optically resolving agent" or
- "contact with a solvent" or
- "alkali salt of the optically active reagent for optical resolution"

are indefinite because it is unknown which are the specific limitations regarding the said alkali salt, solvent or optically active reagent.

In claims 74 and 75 the phrases

- "optically active optically resolving agent"
- "contact with a an alcohol"
- "alkali salt of the optically active reagent for optical resolution"

are indefinite because it is unknown which are the specific limitations regarding the said alkali salt, alcohol or optically active reagent.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4 and 44 to 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kazan et al, US patent 4259521.

Kazan discloses a process for the resolution of (d, l) mandelic acid using optically active 2-amino-1- butanol using water or a lower aliphatic alcohol or mixtures thereof, such method comprising (see col. 1 and 2):

- Reacting (d,l) mandelic acid with optically active 2-amino-1-butanol in the said solvents or mixtures thereof, in order to form the corresponding diastereoisomeric salts
- Separation of the said salts
- Liberation of the optically active substance by conventional acid-base reactions
- Variations to the said process in directed to improve the resolution.

Kazan however, does not discloses the used of 4-amino-2-methyl butane-1-ol as the resolving agent in the said resolution, nor the resolution of 4-amino-2-methylbutane-1-ol using mandelic acid enantiomers as resolving agents.

A person skilled in the art however would be motivated to select enantiomers of mandelic acid- or its derivatives in order to carry out the resolution of racemic 4-amino-2-methyl butane-1-ol via conventional resolution methods base upon the disclosure of Kazan because of the similar chemical structures of 4-amino-2-methylbutane-1-ol and 2-amino-1-butanol. A person skilled in the art would realized that the diastereoisomeric salts formed from a similar amino alcohol and mandelic acid would have similar chemical structure and characteristics to those disclosed by Kazan, especially in reference to the solubilities in water or lower aliphatic alcohols that would facilitates the

diastereoisomers separation and therefore the adjustment of Kazan process but using a similar amino butanol.

No more of routine skill is involved in the substitution of a similar substance in a conventional process already taught in the prior art in order to achieve the enantiomeric resolution via a conventional process and has highly predicted by the said prior art. The optically pure materials are highly valuable as synthetic blocks in organic preparation of more complicated structures.

CONCLUSION

Any inquiry concerning this communication should be directed to Hector M. Reyes whose telephone number is (703) 605-1153. The examiner can normally be reached on Monday to Friday from 8 am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner 's supervisor, Allan Rotman, which telephone number, is (703) 308-4698. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or for regular communication and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Héctor M. Reyes PhD, JD

August 25, 2003.

Alan L. Rotman

ALAN L. ROTMAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600